art would not have used the Pentapharm racemate or L-isomer as a pharmaceutical for treating cancer because Pefabloc uPA is not a "selective" uPA inhibitor but is a strong general serine protease inhibitor. The Pentapharm racemate and (L) isomer are also strong plasmin inhibitors, and therefore are not selective for uPA. At the time the present invention was made, it was commonly believed that anti-invasiveness or therapeutic uPA inhibitors should not inhibit tPA, plasmin or thrombin. Attached to this response is a declaration which was filed in the parent application for the present application. The declaration is signed by Dr. John Foekens and indicates that the Pentapharm catalogs do not indicate that Pefabloc uPA is a "selective" uPA inhibitor. See Declaration of Dr. Foekens paragraph 2. It is particularly noteworthy that the catalogs describe only Pefabloc TH, TH1158, Try 1420 and Tryp as selective inhibitors, and describe the other compounds differently, for example, "Pefabloc®uPA is a low molecular weight synthetic inhibitor for urokinase (uPA)," "Pefabloc®Try can be used to suppress undesired activity of trypsin-like serine proteases during isolation and purification. It can be used in research and industrial processes," and "Pefabloc®PK is employed to inhibit plasma kallikrein (PK) competitively ... is used in chromogenic assays for the determination of factor XIIa activity in plasma with Pefachrome®FXIIa ... suppresses undesired cleavage of the substrate by plasma kallikrein". In view of this, one skilled in the art would know that the catalogs do not describe the racemate or (L) isomer (Pefabloc uPA) as a selective uPA inhibitor useful as a pharmaceutical, but instead indicate that

neither the racemate nor the (L) isomer is a selective uPA inhibitor which would not be expected to be useful in vivo.

Also attached to the present response is a declaration, filed in the parent application and signed by Roger Cohen. Dr. Cohen's and Dr. Foekens' declarations attest that the Ki values disclosed in the tables of the Pentapharm catalogs teach that the Pentapharm racemate and (L) isomer (which are called Pefabloc uPA in the catalogs and WX-UK1 in Dr. Cohen's declaration) are not selective uPA inhibitors but serine protease inhibitors with a broad spectrum of inhibitory activity. See Dr. Foekens' declaration, paragraphs 3-6, and Dr. Cohen's declaration, paragraph 5. As mentioned in Dr. Foekens' declaration, other scientists would have agreed with the finding that one skilled in the art would have known that the Pentapharm racemate or (L) isomer is not a selective uPA inhibitor based on the Ki values disclosed in the tables of the catalogs. See Rockway et al., "Inhibitors of the Proteolytic Activity of Urokinase Type Plasminogen Activator", Current Pharmaceutical Design, 9 (19): 1483-1498, 1484 (2003) (copy attached).

As discussed above, it was generally believed that therapeutic uPA inhibitors should not inhibit tPA, plasmin or thrombin (Dr. Foekens' declaration, paragraph 7; Dr. Cohen's declaration, paragraph 4; Towle et al., "Inhibition of urokinase by 4-substituted benzo[b]thiophene-2-carboxamidines: an important new class of selective synthetic urokinase inhibitor", Cancer Res. 53(11):2553-9, 2553 (1993) (copy attached); and Katz et al., "Structural basis for selectivity of a small molecule, S1-binding, submicromolar inhibitor of urokinase-type

plasminogen activator", Chem Biol. 7(4):299-312, 300 (2000) copy attached).

Bridges, U.S. Patent No. 5,340,833, column 10, lines 35-62, states that

> The compounds described herein inhibit urokinase enzymatic activity in a reversible competitive manner, with high selectivity for urokinase relative to certain other important proteases, including the fibrinolytic enzymes tissue-type plasminogen activator (tPA) and plasmin. In particular, as measured in a plasminogen-linked assay, most of the claimed compounds have IC_{50} values against urokinase of 40 nM to 5 μM. In addition, they are generally 60-800-fold more active at inhibiting urokinase than tPA and are generally 400-10,000-fold selective for urokinase over plasmin. Of 144 benzothiophene derivatives tested to date, 141 exhibit potent and selective urokinase activity and of the 3 available thienothiophene compounds, all exhibit such activity. ...
>
> The selectivity of the instantly-claimed compounds for inhibition of urokinase over inhibition of other proteases such as tPA and plasmin and the fact that they inhibit reversibly prevents them from having thrombogenic properties.

At the time the present invention was made, the selectivity of amiloride (a known urokinase inhibitor used in vivo) for uPA against tPA and plasmin was known to be at least 138-fold greater and the selectivity of B428 (Xing's urokinase inhibitor used in vivo) for uPA against tPA and plasmin was known to be 335 and 1100-fold greater. In contrast to this, the selectivity of the racemate and (L) isomer was known to be only 18~24-fold and 2~3-fold respectively (see Dr. Foekens' declaration, paragraph 8; Towle et al., and Katz et al.). The difference in selectivity between amiloride/B428 and the racemate/(L) isomer as known at the time that the present invention was made, was so great that it is very unlikely that one skilled in the art would have considered the racemate or (L) isomer "functionally analogous" to uPA inhibitors used in vivo (amiloride or B428).

Therefore, the racemate or (L) isomer by itself would not have been classified as a selective uPA inhibitor and would not have been expected to be useful in vivo for the reasons set forth above.

In view of the fact that the Pentapharm product is not selective for uPA, applicants contend that one skilled in the art would not have been motivated to combine Xing and the Pentapharm catalogs to arrive at the present invention. There would not have been a reasonable expectation of success that the racemate or (L) isomer would be usable for cancer treatment because the Ki values in the tables strongly indicate that the racemate and (L) isomer are outside the norm of an uPA inhibitor considered at the time to be useful and acceptable for an anti-invasiveness or anticancer use (see Dr. Foekens' decalration, paragraphs 7 and 8; Dr. Cohen's declaration, paragraph 4). Towle et al., *supra* states that "Since both uPA and its fibrinolytic counterpart tPA share identical specificity for the Arg^{560}-$Va1^{561}$ bond in plasminogen [], most low-molecular-weight protease inhibitors which inhibit uPA also inhibit tPA. Such inhibitors are unsuitable for use as anti-invasiveness drugs due to the potential undesired inhibition of tPA-mediated fibrinolysis. Similarly, anti-invasiveness uPA inhibitors should not inhibit plasmin, since both uPA- and tPA-mediated pathways converge through this enzyme". In view of the above discussion, applicants contend that one skilled in the art would only have considered highly selective uPA inhibitors as potential candidates for treating cancer and would not have considered the Pentapharm research products as potential candidates because they are strong general serine protease inhibitors. One would not have

had a reasonable expectation of success for a pharmaceutical composition containing the Pentapharm racemate or (L) isomer, particularly for an anti-invasiveness or anti-proliferation use, because of the well documented problems of thrombogenic side effects of general serine protease inhibitors. Despite the general belief that strong general serine protease inhibitors would not be useful for treating cancer, the present inventors tested Nα(2,4,6-Triisopropylphenylsulfonyl)-3-amidino-(D,L)-phenylalanine 4-ethoxycarbonylpiperazide, and the L enantiomer thereof and surprising found that they were useful in inhibiting the growth and/or spreading of urokinase associated malignant tumors, metastases and/or lung foci. In view of the fact that this could not have been predicted from the combination of the Pentapharm catalogs and Xing, applicants contend that the presently claimed invention would not have been obvious over the cited prior art and request that this rejection be withdrawn.

Claim 4 was rejected under 35 USC §103(a) over Xing and the Pentapharm 1997 and 1998 catalogs in view of DeVita. DeVita is cited for the disclosure that carcinomas frequently spread and grow in the lymphatic system. DeVita does not suggest or disclose that Nα(2,4,6-Triisopropylphenylsulfonyl)-3-amidino-(D,L)-phenylalanine 4-ethoxycarbonylpiperazide has efficacy for treating cancer *in vivo* despite being a strong general serine protease inhibitor and thus does not cure the above discussed deficiencies in Xing and the Pentapharm catalogs. In view of the above discussion, applicants request that this rejection be withdrawn.

Claims 6-7 and 13-14 were rejected under 35 USC §103(a) as unpatentable over Xing in view of Pentapharm 1998 or Pentapharm 1997 further in view of Medenica. Medenica was cited for the disclosure of a multichemotherapeutic drug regime. Medenica does not suggest or disclose that Nα(2,4,6-Triisopropylphenylsulfonyl)-3-amidino-(D,L)-phenylalanine 4-ethoxycarbonylpiperazide has efficacy for treating cancer *in vivo* despite being a strong general serine protease inhibitor and thus does not cure the above discussed deficiencies in Xing and the Pentapharm catalogs. In view of the above discussion, applicants request that this rejection be withdrawn.

Claims 16-17 were rejected under 35 USC §103(a) as obvious over Xing in view of Pentapharm 1997 or 1998 further in view of Bicher. Bicher is cited for the disclosure of surgery in combination with chemotherapeutic treatments for the treatment of cancer. Bicher does not suggest or disclose that Nα(2,4,6-Triisopropylphenylsulfonyl)-3-amidino-(D,L)-phenylalanine 4-ethoxycarbonylpiperazide has efficacy for treating cancer *in vivo* despite being a strong general serine protease inhibitor and thus does not cure the above discussed deficiencies in Xing and the Pentapharm catalogs. In view of the above discussion, applicants request that this rejection be withdrawn.

Applicants respectfully submit that all of claims 1-19 are now in condition for allowance. If it is believed that the application is not in condition for allowance, it is respectfully requested that the undersigned attorney be contacted at the telephone number below.

In the event this paper is not considered to be timely filed, the Applicant respectfully petitions for an appropriate extension of time. Any fee for such an extension together with any additional fees that may be due with respect to this paper, may be charged to Counsel's Deposit Account No. 02-2135.

Respectfully submitted,

By _____

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